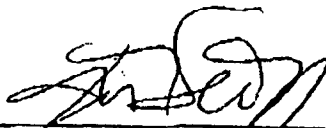


CLINICAL RESEARCH PROTOCOL WHOTI-041

TITLE: Effect of Frequent Daily Use for Four Weeks of a MICRODENT®-containing, Sorbitol-based, Chewing Gum in Reducing Dental Plaque Accumulation When Compared to a Placebo Gum. A Double Blind, Crossover Treatment Design

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Signature of Responsible Party/Date

SPONSOR: Peter P. Walters
WhiteHill Oral Technologies, Inc.
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Hazlet, NJ 07730
(732) 264-0044 (Fax: 0076)



Signature of Responsible Party/Date 10/5/98

A. TITLE: Effect of Frequent Daily Use for Four Weeks of a MICRODENT®-containing, Sorbitol-based, Chewing Gum in Reducing Dental Plaque Accumulation When Compared to a Placebo Gum. A Double Blind, Crossover Treatment Design

B. STUDY PRINCIPAL INVESTIGATOR: Thomas Schiff, D.M.D.

SPONSOR: Peter P. Walters
WhiteHill Oral Technologies, Inc.

C. STATEMENT OF PURPOSE:

The purpose of this clinical trial is to compare in normal human subjects the effect on dental plaque accumulation, with normal brushing, by multiple daily use of a sorbitol-based, sugar-free chewing gum vs. a placebo chewing gum without the active ingredient (trademarked MICRODENT®⁽¹⁾, a proprietary melt-emulsion of dimethicone* in a suitable poloxamer⁽²⁾ which acts as an agent to both clean and modify the tooth surface free energy).

⁽¹⁾ Established as Category I for Safety (Generally Regarded as Safe) by the FDA Subcommittee for Plaque and Gingivitis Ingredient Review

⁽²⁾ FDA reviewed Oral Care/Ingestible ingredients

D. REVIEW OF THE LITERATURE

1. General Overview of Plaque Formation and Effects, L. Menaker, Biologic Basis of Dental Caries, Chap. 5, 11, 12, 14, 16, 18., Harper and Row (1980)
2. Effect of Silicone (simethicone) on Alteration of Tooth Surface Energy and Plaque Attachment, Glanz (1969) and Baier and Glanz (1978)
3. Effect of silicone oil on protein adsorption to hydroxyapatite *in vitro* and on pellicle formation *in vivo*, M. Rykke and G. Rolla, *Scan. J. Dent. Res.*, 1990: 98: 401-11
4. Relevant Patents:
U.S. Patent 4,950,479 "Method of Interrupting the Formation of Plaque"
(24 literature citations, 31 patent references)

U.S. Patent, 4,911,927 "Method and Apparatus for Adding Chemotherapeutic Agents to Dental Floss"

E. EXPERIMENTAL DESIGN AND METHODS

1. Subject Selection

To participate in this clinical study, adults 18-65 years of age must meet the following criteria:

- a. Excluding third molars, each subject must have at least 20 natural teeth present in the mouth.
- b. Have no history of medications that are likely to affect gingival health, i.e. acute hormonal therapy, antisialagogues, calcium channel blockers used as anti-hypertension agents, anti-epileptic drugs and steroids. The use of prophylactic antibiotics or antibiotic usage during the month preceding the study will be grounds for exclusion.
- c. No medical history of rheumatic fever, AIDS, leukemia, cirrhosis, sarcoidosis, diabetes melitis, hepatitis, current pregnancy or any physical condition that limits manual dexterity.
- d. A dental history that includes brushing the teeth at least once a day. Other reasons for exclusion are the presence of gross dental caries; gross neglect of oral hygiene; and the presence of advanced periodontitis, based on a non-invasive examination.
- e. No orthodontic appliances or removable prosthesis.
- f. Should not require premedication with antibiotics for dental appointments, including mitral valve clicks prolapse or other heart murmurs, heart valve replacement and artificial joint.
- g. Sign a consent form.
- h. At time of screening examination, the subject must have a Plaque Index Score of at least 1.8 units (average of all surfaces scored). See Appendix A for criteria.

2. Screening Examination

After review of the subject's medical and dental history, the subject will be examined for a Plaque Index Score of 1.8 units, or greater, (Turesky modification, 1970 of the Quigley-Hein criteria) using a disclosing solution.

3. Experimental Design

Twenty (20) or more subjects will be selected from screening to assure at least 10 subjects/group at completion. This study will use a sequential treatment design wherein the same subjects will be evaluated before and after using each of the products over the specified time periods. The treatments will be four weeks in duration.

A prior series of "range-finding" clinical trials (WHLS-003/004) and a full cross-over design clinical trial (WHLS-005) conducted at Univ. of the Pacific School of Dentistry, established that in a non-brushing protocol with a 48-hour use period and several formula variants of selected **test products** of sugar-free mints and chewing gums demonstrated a reduction in plaque accumulation ranging from about 8% up to 30% vs. the **placebo**. Several of the test products were statistically significant with only 10 subjects in the cross-over design. This design was especially useful for evaluating formula variables *in vivo*.

Plaque accumulation scoring will be performed by only one examiner (the Principal Investigator) throughout the study on a blind basis.

Assessment of plaque accumulation will be made at a baseline examination at the beginning of the study. Each subject will then be given a supragingival, rubber-cup prophylaxis to bring the starting plaque score to zero and product for use over the next four weeks distributed with instructions as follows:

Chew two pieces for 20-minutes three times a day. Times specified are "after meals", or if a regular meal is not taken, then at the approximate time it would have been taken.

At the end of each four week, with brushing, product-use period for each subject, the plaque scores will be assessed for the "final" reading on that period's product. Baseline and all final examinations will be performed within the same one-hour time period of the respective day.

4. Protocol

Patients will be instructed to brush their teeth according to their normal oral hygiene patterns, using their regular brush and toothpaste except subjects will be screened and rejected for prior use of antimicrobial toothpaste such as Total®. They will be instructed to not use any mouth rinses. They will be instructed to use only the gum provided at the times specified.

SCHEDULE

Day 1

Subjects have refrained from brushing
12 hours before Baseline Scoring

BASELINE EXAMINATION

Perform a standard rubber cup prophylaxis
to reduce initial plaque index to zero

PROPHY

Subjects are divided into two groups and
assigned either the placebo or test gum for
the first leg of the crossover design

Subjects are given coded packets
containing sufficient quantities of the
appropriate product for the full test period
and instructed as to use

Subjects are instructed concerning product use
and specified restrictions on normal hygiene.

Day 28 (end of first leg of gum crossover)

Subjects have used specified product
with normal oral hygiene since Day 1

FINAL EXAMINATION I

Subjects return to their normal hygiene
for the next 7 days

WASH-OUT PERIOD

Day 35 (end of no chewing gum control period)

Subjects with normal oral hygiene since Day 28

Perform a standard rubber cup prophylaxis
to reduce initial plaque index to zero

PROPHY

Subjects are assigned the gum not used
from Day 1-28, either the placebo or test gum,
for the final leg of the crossover design

Subjects are instructed concerning product use
and specified restrictions on normal oral hygiene

Day 63 (end of second crossover gum period)

Subjects have used specified product
with normal oral hygiene since Day 35

FINAL EXAMINATION II

Subjects instructed to return to normal habits

TIMES OF USE

1. After breakfast (if no meal taken then by 9 a.m. each day)
2. After lunch (if not meal taken then between 12 noon and 1 p.m.)
3. After dinner (if no meal taken then between 7 and 8 p.m.)

Compliance will not be monitored, but patients will be instructed to return all used product packets.

The clinical coordinator will provide each subject with appropriate product packages marked with the appropriate code. The Sponsor is responsible for breaking the code. Returned product will be examined only if final examination data presents anomalies which might be explained by examining returns.

5. **Subject Protection/Liability**

Since the procedures to which subject volunteers will be exposed are not different from those ordinarily used by each clinical site in routine evaluation and treatment of patients, the patient protection measures ordinarily employed by each clinical site with respect to prospective and accepted patients are sufficient. Informed consent of each subject accepted into the study will be recorded on a form customarily used by that clinical site and acceptable to its I.R.B. (See Appendix E-H). This will be included in the subject's clinical file along with his/her medical history form and data collected in the course of the study. Patients will be remunerated as deemed appropriate by the clinical site.

6. **Principal Investigator's Duties**

The Principal Investigator shall manage the study at this site to provide for proper blinding, orderly and professionally responsible handling of subjects and tests or examinations, accurate compilation of data, timely and accurate reporting to the Sponsor, and protection of Subjects' rights.

7. Monitoring

Employees, consultants, or other appropriately qualified agents of the Sponsor shall monitor the activities at each clinical site to assure adherence to the protocol and protection of Subjects' rights.

8. Data Analysis

Appropriate statistical methods will be employed by the Sponsor to evaluate correlations among the parameters of the study. At minimum, correlations between plaque accumulation means will be determined. Comparisons will be made between the means of final examinations after the use of **placebo gum** and **test gum (with MICRODENT®)** product groups respectively. Correlation with incoming **baseline** means will be made to assure relevancy of test group data. Other exploratory analyses, both parametric and non-parametric, may be employed.

APPENDIX A

Turesky Modification of Quigley Hein Plaque Scoring Method

- | | | |
|---|---|--|
| 0 | = | No plaque. |
| 1 | = | Separate flecks of plaque at the cervical margin of the tooth. |
| 2 | = | A thin continuous band of plaque (up to one mm) at the cervical margin of the tooth. |
| 3 | = | A band of plaque wider than one mm but covering less than one-third of the crown of the tooth. |
| 4 | = | Plaque covering at least one-third but less than two-thirds of the crown of the tooth. |
| 5 | = | Plaque covering two-thirds or more of the crown of the tooth. |

1. Quigley GH & Hein JW JADA 65-26, 1962
2. Turesky, S. et. al. J. Periodont. 41:41, 1970

If fleck of plaque (line angles or anywhere) is NOT in contact with gingiva - score it ZERO.

If it CONTACTS gingiva - same fleck is scored 1.

If 1 mm or less band but with small break - Score 2.

If any portion of band has area of more than 1 mm and/or less than 1 mm although it is not a continuous band (see illustration below) - score it 3.

APPENDIX B

STUDY QUESTIONNAIRE

PLEASE PRINT

Name _____

Telephone (Office) _____ (Home) _____

Office/Lab Address: _____ (Room) _____

Social Security # _____

Home Address: (Street) _____

(City) _____

(State & ZIP) _____

Gender (sex) _____

Age _____

Race _____

How many times per day do you brush? _____

Have you ever had a heart murmur? Yes _____ No _____

Have you ever had hepatitis? Yes _____ No _____

Do you have diabetes? Yes _____ No _____

Are you currently pregnant? Yes _____ No _____

APPENDIX C

University of the Pacific School of Dentistry Informed Consent - Chewing Gum Study

If accepted for this study, you will participate in a three month investigation of the efficacy of a series of chewing gums on reducing plaque accumulation with your normal tooth brushing habits. The chewing gums contain only ingredients that are commercially available and FDA approved. You are asked to participate because you are an apparently healthy adult with most of your natural teeth. You must come for a total of four examinations - at the beginning and at the end of the three one month product use periods. A tooth cleaning will be performed just after each of the first three examinations. The teeth and gums will be examined and a removable stain to disclose plaque (germs) will be applied to the teeth. It is estimated each examination will require 10-15 minutes. You will use the chewing gum in a normal fashion 3 times a day during the test period. At the conclusion of each four week segment of the study you will be paid \$150, provided you miss no appointments **and return all unused gums and packets at the end of the study.**

Assignment of products the first and third months will be made on a random basis. During the study, you will brush as you have always done but you cannot use an antimicrobial toothpaste, a therapeutic mouthrinse, mints or gums other than those provided. Routine dental treatment, other than cleanings, may be done during the three months of the study. You should report to us any antibiotics or other prescription drugs taken during the study.

Your decision not to participate in the study or to withdraw after the study starts will not prejudice your future relations with the University of the Pacific School of Dentistry.

Your signature below indicates that you understand that UOP has made no provision for monetary compensation to you in the event of physical injury resulting from the research procedures. Should physical injury occur, medical treatment is available, but treatment is not provided free of charge.

If you have any questions, we expect you to ask us. If you have additional questions later, Dr. Schiff can be reached at the Department of Radiology, University of the Pacific School of Dentistry.

You are making a decision whether or not to participate. Your signature indicates you have decided to participate after having read the information above.

Signature _____ Date _____

Signature of Investigator _____

APPENDIX D

RESEARCH AGREEMENT

Between

WHITEHILL ORAL TECHNOLOGIES, INC.

And

UNIVERSITY OF THE PACIFIC SCHOOL OF DENTISTRY

THIS RESEARCH AGREEMENT, made this day, by and between WhiteHill Oral Technologies, Inc. (hereinafter referred to as "the Sponsor") and the University of the Pacific School of Dentistry (hereinafter referred to as "the University").

NOW THEREFORE, THE PARTIES HERETO AGREE AS FOLLOWS:

ARTICLE I: STATEMENT OF WORK. The University agrees to use its best efforts to perform the research program entitled "Effect of Frequent Daily Use for Four Weeks of a MICRODENT®-containing, Sorbitol-based, Chewing Gum in Reducing Dental Plaque Accumulation When Compared to a Placebo Gum".

ARTICLE II: PRINCIPAL INVESTIGATOR. The research will be supervised by Dr. Thomas Schiff. If, for any reason, Dr. Schiff is unable to serve as Principal Investigator, and a successor acceptable to both the University and the Sponsor is not available, this Agreement shall be terminated as provided in Article VI.

ARTICLE III: PERIOD OF PERFORMANCE. The performance of this Agreement shall begin October 5, 1998, and shall not extend beyond the estimated completion date of December 12, 1998, unless the period is further extended by amendment to this Agreement. However, the University shall have no liability to Sponsor, or shall it be in default under this agreement if performance is delayed or prevented by any cause beyond the University's control.

ARTICLE IV: REIMBURSEMENT OF COSTS. In consideration of the foregoing, the Sponsor will reimburse the University for all costs (direct and indirect) incurred in the performance of the research which shall not exceed the total estimated project cost of \$30,000 without written authorization from the Sponsor.

ARTICLE V: PAYMENT. Payment shall be made to the University by the Sponsor in advance on the following schedule:

1. \$15,000 payable by October 5, 1998; and
2. \$15,000 payable on delivery of top line data.

ARTICLE VI: TERMINATION. Performance under this Agreement may be terminated by the Sponsor upon sixty (60) days written notice; performance may be terminated by the University if circumstances beyond its control preclude the continuation of the research. Upon termination, the University will be reimbursed as specified in Article IV for all costs and non-cancelable commitments incurred in the performance of the research prior to the termination date of the Agreement. Such reimbursement is not to exceed the total estimated project cost specified in Article V.

ARTICLE VII: PUBLICATIONS. The University will be free to publish papers dealing with the results of any research under this Agreement. Where appropriate the University will give a copy of the paper to the Sponsor at least thirty (30) days prior to the intended submission for publication to allow the Sponsor to review for patent purposes and/or for inadvertent disclosure of the Sponsor's proprietary data.

ARTICLE VIII: SPONSOR PROPRIETARY DATA. The free dissemination of information is an essential and long-standing policy of the University. However, under exceptional circumstances, the University recognizes that it may properly hold in confidence data supplied by a sponsor which the University considers essential for the conduct of a research program. Accordingly, the University's acceptance and use of any proprietary data which may be supplied by the Sponsor in the course of this research project shall be subject to the following:

- (a) The data must be marked or designated in writing as proprietary to the Sponsor.
- (b) The University retains the right to refuse to accept any such data.
- (c) Where the University does accept such data as proprietary, it agrees to exercise all reasonable efforts not to publish or otherwise reveal the data to others without the permission of the Sponsor, unless the data has already been or is subsequently published or disclosed publicly by third parties, was previously known or subsequently independently discovered by the University without the benefit of the proprietary data, or is required to be disclosed by order of a court of law or other governmental authority. It is agreed that such reasonable efforts by the University or other governmental authority will be in lieu of all other obligations or liabilities of the University relative to proprietary data.

Research Agreement

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ARTICLE IX: PATENTS. Title to any invention or discovery made or conceived by University personnel in the performance of the research shall remain with the University provided, however, that the University shall grant to the Sponsor the rights of first negotiation to obtain a license to make, use and/or sell such invention or discovery, with the right to sublicense, under reasonable terms. The terms of exclusivity, fees and royalty rates will be negotiated with the University at the time the invention or discovery is made, provided further, however, that this right must be exercised by the Sponsor by notice in writing to the University within three (3) months from the date the invention or discovery is first disclosed to the Sponsor.

If the University files patent applications or otherwise obtains patent rights which relate to the licensed products of this Agreement, and if the Sponsor shall obtain rights to a further option or a license under such patent rights as are set forth in this section, the Sponsor shall bear the reasonable costs for the preparation, filing and prosecution of the patent applications under which the Sponsor accepts a license, but in no case beyond an appeal to and a decision by the United States Patent and Trademark Office Board of Appeals, unless the Sponsor specifically agrees otherwise in writing.

ARTICLE X: USE OF NAMES. Neither party will use the name of the other nor the name of any of its employees in any form of publicity without the written permission of the other. In the case of the University, permission of the University Relations Office is required.

ARTICLE XI: ASSIGNMENT. Neither this Agreement nor the rights herein granted to the University shall be assignable or otherwise transferrable by the University without the Sponsor's prior written consent, except that the University may assign or otherwise transfer this Agreement or the rights granted herein to a University-related, non-profit research foundation. Such assignment shall not relieve the University of its obligations hereunder and the Sponsor may ask for reasonable assurances to such effect. Any such assignee for the University shall be bound by the terms hereof as if such assignee were the original party hereto.

ARTICLE XII: INDEPENDENT CONTRACTOR. In the performance of this agreement the University shall be an independent contractor. Neither party is authorized to act as the agent of the other and neither shall be bound by the acts of the other.

ARTICLE XIII: APPLICABLE LAW. This agreement shall be governed by the laws of the state of California.

UNIVERSITY OF THE PACIFIC
SCHOOL OF DENTISTRY

By Dr. Thomas Schiff 10/5/98
(date)

WHITEHILL ORAL
TECHNOLOGIES, INC.

By Peter P. Walters 10/5/98
(date)

MICRODENT®

SUMMARY OF SAFETY CONSIDERATIONS

NOTICE:

The FDA Subcommittee on Plaque and Gingivitis has specified that the ingredient MICRODENT® be designated Category I for Safety (Generally Regarded As Safe). The details provided below were included in the Expert Panel's deliberations.

DEFINITION: MICRODENT® is defined in submissions to the above Expert Panel as "an emulsion of polydimethylsiloxane (dimethicone or PDMS) in a suitable poloxamer." The version of MICRODENT® in the proposed study is composed of 65% Poloxamer 407 (Pluronic F-127®, Food Grade) and 35% dimethicone (2.5 million cs).

I. Included in WhiteHill filing with FDA "call-for-data" on Plaque and Gingivitis Ingredients

A. Summary of Toxicity of dimethicone and Dow Corning Drug Master File. (J. of Ind. Hygiene and Toxic. Vol. 30, No. 6, pp 332-352)

1. General Observation:

Toxicity decreases as viscosity (cs) and molecular weight increases. Data below relates to 350 cs dimethicone such as is used in OTC antacid, anti-gas products. Typical dose in such products is 40-80 mg. with 3-5 doses per day allowed. The maximum ingestible dimethicone from the chewing gum formulation under consideration is about than 2 mg per piece. The protocol calls for 5 pieces per day or 10 mg per day total consumption. The dimethicone in these gums is 2.5 million cs. It is well established in the literature that oral toxicity is greatly reduced with increasing molecular weight or viscosity (increased molecular weight is commercially expressed in the more easily measured parameter of viscosity).

2. Eye and Skin Irritation:

Direct instillation of 100% dimethicone in rabbit eyes produced only transitory irritation with the eyes returning to normal after 24-48 hours. No evidence of corneal damage. Humans accidentally exposed to same dosage report a temporary feeling described as being somewhat like wind burn.

Dimethicone repeatedly (20 times in a month) applied to the ears and shaven abdomens of rabbits produced no irritation.

3. Ingestion

Single dosages of up to 50 ml (about 45 grams) per kilogram in rats failed to elicit any fatalities or other response other than transient laxative effect. Repeated (20/month) doses of up to 20 grams/kg produced no evident toxicity or changes in organ weights.

B. Summary of Poloxamer (BASF Pluronic F127 or F108) Toxicity
(BASF Drug Master File)

1. Acute Toxicity:

Oral LD50 is greater than 10 g/kg (classified Practically Non-toxic) in rats, 15 g/kg in rabbits.
Minimally to non-irritating in eye or skin tests with rabbits.

2. Ames Test: Negative.

3. Chronic Toxicity:

Rats: 90 day, fed in diet up to 1.5 g/kg/day
No deaths or organ damage

Six week, fed in diet 5-30% of diet weight
No deaths, diarrhea weakness at >10%.

Two generation reproduction, fed in diet up to 2.5%
Did not alter ability to mate and reproduce.

Dogs: 90 day, fed in capsules up to 1.5 g/day
No deaths or organ damage.

C. WhiteHill and Licensees Experience with Microdent™
Formulated into Products.

1. Hamster Cheek Pouch Study

Baby Orajel Gum and Tooth Cleanser (2% Microdent in gel form), dosed at 0.1, ml 3 times/day, 20 days/month. No significant deviations from histologic morphology. No treatment related changes in blood count or blood chemistry.

2. Oral LD50 of Baby Orajel Gum and Tooth Cleanser

No mortality at 10 g/kg in rats.

3. Soft Tissue Involvement during various clinicals.

In 24 completed clinicals, ranging from 30 days with multiple daily applications from floss, toothpaste, spray and mouthrinse to 10 times/day in a mint to six weeks at twice a day flossing:
No oral mucosa or soft tissue involvement observed in any patient.

II. Commercial History of Microdent Usage.

NOTICE: There has been no consumer complaints attributable to the ingredient MICRODENT® in any of the commercial products in use since 1991.

1. Dunhall Pharmaceuticals, Inc.

Original version of floss sold via Dentists since 1991. No record of consumer complaints or negative professional examinations. Original version was a "straight filament" floss with 40 mg/yd of ingredients containing 62% Microdent.

2. NuSkin International

Marketed via direct door-to-door sales since November 1993, Nuskin has purchased 800,000, 60 yd packages of a "straight filament" floss containing 80 mg/yd of ingredients containing 62% Microdent and over 1 million unit dose packets. Order patterns suggest about 60% are in use by consumers as of this date. In addition, about 125,000 packages of a "Kids Floss" similar to containing 100 mg Microdent per yard has been sold.

3. Johnson & Johnson

REACH® *Gentle Gum Care* Dental Floss is internationally distributed and enjoys a major market share in the USA. 1.3 billion yards have been shipped containing 90 mg/yd of MICRODENT®.

4. Del Pharmaceuticals, Inc.

Baby Orajel Gum and Tooth Cleanser® containing 2% microdent and dosed at 100-300 mg/day has been sold nationwide for use by infants since 1991.

5. Mouthspray, Mouthwash, Toothpaste

Over 1 million units of a mouthspray branded Take-5™ was sold nationwide in major chain drug and supermarkets from 1986-90.

Dunhall Pharmaceutical has marketed all three forms of Microdent via dentists since 1990. Nuskin International has distributed over 500,000 of each since November 1993.

Nuskin International has distributed several million units each of Mouthspray, Mouthwash and Toothpaste, including a toothpaste and Dental Floss for children

Certification: The above information is true and accurate according to the best information available to me as of this date.


Peter P. Walters

President, WhiteHill Oral Technologies, Inc.
Manufacturer of MICRODENT®

10/5/98
Date